

# Therapeutic Synergies in the Fight Against Cancer

*Surgery, radiation, and chemotherapy are the mainstays of oncology, composing most of the first-line standard of care for virtually all cancers. As newer strategies are introduced into the therapeutic arsenal, particularly for earlier stages of disease, they are almost always tested in addition to, rather than instead of, the standard of care. Not only are these newer strategies proving effective in combination with the older methods, but surprisingly strong synergies are emerging among them. Several CCR investigators are finding ways to exploit these synergies for the benefit of patients.*

## Vaccine Trials and Tribulations

"Cancer vaccines have had a hard time over the last several years," remarked James Hodge, Ph.D., Senior Scientist in the Laboratory of Tumor Immunology and Biology. Hodge described a series of failed Phase 3 clinical trials for cancer vaccines as monotherapies against late-stage disease that forced companies like Cell Genesys and Therion Biologics out of business. One reason these trials failed, Hodge believes, is that cancer vaccines are probably least effective as a last resort against late-stage disease. Studies have shown that the immune response is

blunted in patients that have recently undergone chemotherapy or have had several courses of chemotherapy prior to receiving a vaccine.

As the safety of cancer vaccines has been established over time, however, clinical researchers have been able to administer vaccines to patients closer to the time of diagnosis. In such patients, where a clear standard of care exists, the natural strategy is to test a new therapy in combination with existing care. But first, the safety of any novel combination must be established in preclinical models.

"Combining radiation and vaccine therapy in our preclinical models was a real eye-opener," said Hodge.

He and his colleagues designed an experiment in which the vaccine was essentially set up to fail on its own—they injected tumor cells into a mouse engineered to express the human tumor antigens targeted by the vaccine and then withheld the treatment until eight days later. As expected, neither vaccine alone nor radiation therapy alone was sufficient to reduce the large tumor burden achieved in the meantime. However, in those mice given a combination of radiation and vaccine, 60 percent were cured outright. "That's something we hardly ever see in preclinical models," said Hodge. "And it was all we needed to move forward into the clinic."

## Radiation and Immunotherapy—The Theory

Radiation works by producing cellular damage that evokes programmed cell death. “The oxidizing radicals damage cancer cells, but also the normal tissues as well,” explained Aradhana Kaushal, M.D., Staff Clinician in the Radiation Oncology Branch. “The idea is that the normal cells can repair themselves, but of course they are affected by radiation too, which is why we see side effects.” Radiation oncologists work on trying to limit the effects of radiation to cancer cells, whether by physically constricting the beam of radiation to focus on a tumor mass or by co-administering compounds that will either enhance the vulnerability of tumors or reduce the vulnerability of healthy cells (see “Radiating Change,” *CCR connections* 3(1)).

Cancer vaccines work by training the immune system to recognize and destroy cancer cells. Cancer cells have distinct molecular markers—antigens—that, when processed by specialized antigen-presenting cells (APCs), help the immune system to recognize and target the cells bearing them for destruction by cytotoxic T cells. APCs are drawn to diseased or damaged cells because the cells give off stress signals that let the system know that they need to be cleared away. It makes sense, therefore, that levels of radiation that may not be sufficient to kill cancer cells outright might be sufficient to boost signs of stress and disease that the immune system can recognize.

James Gulley, M.D., Ph.D., Head of the Clinical Trials Group in the Laboratory of Tumor Immunology and Biology, is enthusiastic about a trial he is currently running to combine vaccine therapy with a form of radiation therapy in patients with metastatic prostate cancer who have run out of proven therapeutic options. The radiation, in this case, is coming not from an external beam but from a compound, samarium-153, that contains a short-lived isotope.



James Hodge, Ph.D.

(Photo: R. Baer)

Samarium-153 is not very effective in killing tumor cells. Instead, it is given to patients to ease the pain of metastatic bone cancer. The drug accumulates in areas of the bone that contain cancer and provides pain relief. Hodge has done the preclinical studies, demonstrating that the radiation delivered by samarium-153 has a similar immune-boosting effect as beam radiation in a cell culture model. Gulley is taking the work into the clinic, comparing tumor progression in patients who receive samarium-153 with or without their prostate cancer vaccine. “I am really quite intrigued by the results so far,” Gulley said, cautioning however that the data are not yet mature for his randomized Phase 2 trial.

### Timing Is Everything

Chemotherapy is a blunt instrument, killing any cell that is dividing rapidly, including cells of the immune system. And unlike radiation, it

Chemotherapy and immunotherapy can also have synergistic effects.

is seldom focused on a particular tumor or organ and thus usually also disrupts the immune system. But Gulley and Hodge are finding that, if delivered correctly, chemotherapy and immunotherapy can also have synergistic effects.

A strong hint on the importance of timing in vaccine trials came from the results of a human trial in which patients with prostate cancer that did not respond to hormone therapy were initially given either of two treatments—an experimental prostate cancer vaccine or an FDA-approved androgen receptor



antagonist, nilutamide. Untreated, these patients would likely develop metastases within a year. Neither treatment improved the odds much: patients who were randomized to receive the vaccine alone progressed similarly to those who received the nilutamide. “However, the interesting thing was that after six months, patients who had rising PSA [prostate-specific antigen] levels but no metastases visible on scans could add in the other treatment,” explained Gulley. Surprisingly, the patients that started out on vaccine first and then added nilutamide after six months had much slower disease progression and actually lived longer.

“It seems like the patients that start out with vaccines first do better on a subsequent therapy, said Gulley. “We have seen many anecdotal reports and retrospective subset analyses that support this finding.” The group also performed a trial in which patients with prostate cancer received vaccine alone or with the standard-of-care chemotherapeutic agent docetaxel. Both patient groups had similar results (the disease progressed after three months), but for patients who received vaccine alone and then were switched to the combination after initial assessment, progression on chemotherapy was delayed another three months.

“I attribute it to the fact that you are generating an immune response that can be around for a long time. Most of the time, you think about treatment as only effective around the time of administration, but vaccines can exert continued effects on growth for much longer,” said Gulley.

Jeffrey Schlom, Ph.D., Chief of the Laboratory of Tumor Immunology and Biology, pointed out that several factors may be involved in early vaccination. “If you get the vaccine on first, the immune system may be responding with circulating T cells, but they may not be strong enough to kill on their own. If you give radiation

“Maybe you do better if you get the vaccine first.”

or chemotherapy, it could act as a boost or change the cancer cells to make them more susceptible.” The team is getting ready to open a large randomized cooperative group trial to specifically compare the effects of docetaxel given alone with the effects of docetaxel given after a series of vaccinations. “This will be the first prospective study evaluating the concept that maybe you do better if you get the vaccine first.”

### Don't Forget the Blood Supply

Vaccines, of course, are not the only rising stars in the world of anti-cancer strategies. Ever since the pioneering work of Judah Folkman, M.D., the tumor blood supply has been an important target for cancer research. William Dahut, M.D., Clinical Director of CCR, has studied angiogenesis drugs in prostate cancer for many years.

“We started with thalidomide, which probably has some anti-angiogenesis properties,” remembered Dahut. “We showed in a small randomized trial that if we added thalidomide to docetaxel, it improved survival over docetaxel alone.” When bevacizumab (Avastin) came along, his group combined it with thalidomide as an addition to the standard of care in a single-arm Phase 2 study. “We had probably the highest response rate of any trial in that population. In 90 percent of the patients, PSA levels fell by 50 percent and the time to cancer progression was about 18 months, which was pretty much equal to the overall survival time historically.” The team has since replaced thalidomide with a related drug, lenalidomide, which has a better side effect profile, and are conducting additional trials. “We have treated about 11 people so far and I think virtually everyone has responded.”



Jeffrey Schlom, Ph.D., and James Gulley, M.D., Ph.D.

(Photo: R. Baer)

“Anti-angiogenesis—I’m not even sure what that means,” noted Dahut. “You don’t necessarily see blood vessels disappear. Usually, they are called that because they interfere with things like VEGF, which are shown to be involved in angiogenesis. But it is less clear that’s why these drugs have activity. They could be improving drug permeability, for example.” Regardless, the consensus seems to be that, in most cases, angiogenesis inhibitors work best in combination with other agents. Although initially studied on their own, they were mostly found to have minimal activity in solid tumors, with kidney cancer being the notable exception.

### One Big Happy Family?

Vaccines may soon join angiogenesis inhibitors in commercial triumph. Hodge, Gulley, Dahut, and their colleagues are optimistic because of the recent launch of a revolutionary prostate cancer vaccine, custom-made for each individual patient. Dendreon is the first company to receive FDA approval for a cancer vaccine. Their vaccine—Provenge—also targets prostate cancer, but is designed against a different antigen associated with the cancer. “It will open the floodgates,” predicted Hodge, who is keen to try their own vaccine in combination with Provenge.

“Combinations are where we’ve seen our strongest clinical effects,” noted Hodge, even though the mechanisms may not always be completely clear. In both preclinical and clinical observations, the team has noted, for instance, that their vaccine—which is designed to elicit an immune response to a particular antigen found on prostate cancer cells—in combination with radiation elicits a much broader immune response (i.e., to multiple antigens) than expected. “That was the tumor itself educating the immune system about which antigens are most important.” This antigen cascade is



(Photo: R. Baer)

William Dahut, M.D., confers with a patient.

not only a tool to help the researchers discover better antigen targets, but also may allow the immune system to recognize heterogeneous tumors and distal metastases on its own.

“We look at vaccines as part of an immunologic platform, which involves using other immune stimulators in combination,” concluded Schlom. “But we also look at this as a program in immuno-oncology where vaccines are integrated with standard oncology or new oncology drugs.”

Recently, Hodge and his colleagues were invited by the journal *Molecular Biosystems* to write an article in which they speculated about the potential synergy between immunotherapy, radiation, and angiogenesis inhibitors. “We haven’t tried that combination,” explained Hodge. “But bevacizumab is very quickly working its way into the standard of care—for instance, in colorectal cancer.” So it is worth exploring how all the

players might work together. The responses they have received from the community to the article have been gratifyingly positive.

To learn more about Dr. Hodge’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=hodge>.

To learn more about Dr. Gulley’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=gulley>.

To learn more about Dr. Schlom’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=schlom>.

To learn more about Dr. Dahut’s research, please visit his CCR Web site at <http://ccr.cancer.gov/staff/staff.asp?Name=dahut>.